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10/816,798	04/02/2004	Manne Satyanarayana Reddy	BULK3.0-047	9941

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EXAMINER
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CHANG, CELIA C

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 10/816,798  
Filing Date: April 02, 2004  
Appellant(s): REDDY ET AL.

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Lee Banks  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed April 7, 2008 appealing from the Office action mailed May 7, 2007.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The inclusion of claim 1 in the final rejection was inadvertent because claim 1 has been canceled. Correction is hereby made.

(A) Claims 2-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Imai et al. US 5,985,864. The original rejection was applied to the currently amended claims 2-6.

(B) Claims 2-6, 8-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Imai et al. US 5,985,864 in view of Doelker, Wikipedia, Davidovich or US Pharmacopia.

(C) Claim 8-12 are objected to under 37 CFR§1.75(c) being of improper dependent form for failing to further limit the subject matter of the base claims.

### **(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

### **(8) Evidence Relied Upon**

5,985,864                                      Imai et al                                      11-1999

\*Davidovich et al. "Detection of polymorphism....." Am. Pharm. Review (2004) p. 10, 12, 14, 16, 100.

\*Doelker "Crystalline modification in polymorphic....." Ann. Pharm. (2002) p.161-176 (translation p.1-36)

\*US Pharmacopia #23, National formulary #18 (1995) p.1843-1844.

\*Wikipedia "polymorphism trivia" encyclopedia on internet p.1-2 (2006)

\*Exhibit I-III

\*Berstein "Polymorphism in molecular crystals" p.115-118 (2002)

### **(9) Grounds of Rejection**

The following grounds of rejection are applicable to the appealed claims:

(A) Claims 2-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Imai et al. US 5,985,864. The original rejection was applied to the currently amended claims 2-6.

See col. 7, line 13, crystalline 1-benzyl-4-[(5,6-dimethoxy-1-indanon-2-yl)methyl]piperidine hydrochloride with M.P. 229°C and process of making at col. 8, lines 20-24 or col. 15, example 18.

Please note that the instant claims being drawn to donepezil hydrochloride crystals having substantially X-ray powder diffraction as depicted in figure 1 is anticipated by figure 3 product of Imai et al. '864. A comparison of substantial diffraction pattern was made in Exhibit I, which is hereby attached for applicant's convenience. Upon similar para-scaling, substantial IR, TG and DSC can be found between the instant figure 2 vs figure 8, instant fig. 3 and fig. 4 vs. figure 13 (now placed together as exhibit II and III). Substantial patterns can be identified as in Exhibit I-III. Therefore, anticipation was found for all the claims.

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The only difference between the process of claim 6 and the example 18 is the drying or preheating to dissolve the starting material since such is not the critical step in crystallization and the prior art apparently had a “solution” of donepezil free base in ethanol, anticipation was found. In addition, in a small section of examples 16-23, the heating step was well delineated in example 23, therefore anticipation was found based on small genus with clearly delineation. Ex parte A 17 USPQ2d 1716.

(B) Claims 2-6, 8-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Imai et al. US 5,985,864 in view of Doelker, Wikipedia, Davidovich or US Pharmacopia.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Determination of the scope and content of the prior art (MPEP §2141.01)

Imai et al. ;864 disclosed anticipatory product as claimed in claims 2-5 made by process of claim 6, see figures 3, 8, 13 and examples 18 and 23 and clearly delineation of anticipation supra.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the dependent claims 8-12 wherein variation of solvent system was employed in the process of crystal preparation is generically taught by Imai et al. ‘841 and exemplified in examples 16-23 wherein the variation of preheating, solvent mixtures, drying temperature were clearly delineated.

Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art in possession of the US 5,985,864 reference is in possession of the instantly claimed variations. The well delineated variation in the reference gives clearly guidelines on the suitable conditions one can optimize to obtain the desirable crystal form.

One having ordinary skill in the art in possession of the prior art references is in possession of the instant claims because the prior art disclosed the same pure compounds 1-benzyl-4-[(5,6-dimethoxy-1-indanon-2-yl)methyl piperidine hydrochloride and its multiple crystalline forms with at least one having the substantial patterns (see exhibit I-III) of physical properties as the instant claims (see 102 rejection supra). Applicants allege that there are differences between the prior art data and the instantly claimed data. It is well recognized in the

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art that X-ray diffraction patterns may have different appearance due to artifacts (Davidovich) and small differences in X-ray diffraction may be due to solvent, thus must be carefully evaluated whether it is true new polymorph by factual comparison (US pharmacopia). If there is any true discrepancy which are not artifacts between laboratories or experimental conditions, such difference must be supported by competent comparisons based on factual evidence. Mere arguments by attorney is entitled to little weight. In re Lindner 173 USPQ 356.

Further, the opinion of artisan in the field is that "more than half of the pharmaceutical compounds exhibit polymorphism"(Doelker summary) and "...every compound has different polymorphic forms and that in general the number of forms known for a given compound is proportional to the time and money spent in research on that compound" (Wikipedia). Thus, variation is expected and variation, unless supported by factual comparison, does not support new form but obvious variation of the old form.

(C) Claim 8-12 are objected to under 37 CFR§1.75(c) being of improper dependent form for failing to further limit the subject matter of the base claims.

The dependent claims are drawn to scope "comprising" alcohol or ether which is broadening of the base claim 2 which is a polymorphic form and can be made only using alcohol or ether as the solvent.

#### **(10) Response to Argument**

##### a. Rejection under 35 USC 102(b)

Appellants argued that there are differences in physical data between the claims and prior art in :

X-ray-----the 11.5 peaks is absent in prior art and the 6.5 peaks is not in form VI;  
thermo-data--prior art has 229-231°C, instant form VI has 222-225 °C;  
processing steps--- prior art reaction in ice bath, instant process at room temperature.

##### **It is the Examiner's position:**

In so far as the *powdered* x-ray diffraction pattern is concerned, it has been clearly made of record that a side by side comparison of the instant pattern and the prior art pattern showed **substantial** similarity. Initially, appellants' attention is drawn to that the pattern is "substantially" as depicted in figure 1. As it has been made very clear of record that *powdered* x-ray diffraction pattern have well recognized to have artifacts for which suppression of peaks is not uncommon. A state-of-the art reference by Bernstein is hereby provided. Bernstein described that "the preparation of samples for powder diffraction can lead to variations and inconsistencies among measurements..." (p.115) and in an extreme case, as depicted by Bernstein p.118, very substantial suppression of peaks from a single crystal x-ray can occurred in the "powdered" x-ray pattern. Therefore, the extensive similarities in physical data between the prior art and the instant application (see exhibit I, II and III) would meet the *state of the art* standard as being substantially identical in measurements. Please note that in so far as the Bernstein standard is

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concerned, if one peak is the same it could be the same crystal. Normally, even in not so extreme cases, the intensity of the peaks can vary tremendously in a powdered diffraction pattern. In the instant case, visual comparisons in X-ray, IR and DSC observed in the record, all provided much similarity to meet the substantially same requirement.

In so far as the thermo data is concerned, it is very confusing as to what is the thermo-data for the claimed form VI, please note that the fig. 4, DSC of the instant form VI has a peak of 229.85 °C, with endset at 232.25°C which is very similar to the prior art fig. 35 (see exhibition II), wherein only the endset of 232.0 °C was marked. The 222-225 °C described on page 8 was associated with decomposition (see page 8, lien 4). It is common understanding by chemists that broad melting points with decomposition ordinarily relates to impurity of the product. Again, appellants attention is drawn to “substantially” having thermogram as figure 4 which is compared to figure 35 of the prior art to be substantially similar. These other decomposition and melting issues discussed by appellants are not required by the claims (see only figures 1,2,3,4 are the scope of the claims), however, conflicts between 222-225 °C on page 8 and figure 4 of the instant application should be clarified.

In so far as the processing steps are concerned, appellants’ description of the process is completely erroneous. Appellants process using "diluted" free base and hydrochloric acid at 20-35 °C, the prior art did use ice bath, but that is because the dissolved free base was acidified with “concentrated” hydrochloric acid. Just because an ice bath was used to cool the reaction, does not mean 0 °C was the reaction mixture because subsequent process was maintained at room temperature. The cooling is in the preparation of a donepezil hydrochloride solution which does not contain either form III (prior art) or form VI as claimed and the resulting temperature is the same as the claims i.e. room temperature 25 °C. The critical steps in crystal formation are identical, that is *stirring the solution overnight at room temperature* (\*864, col. 15 line 54-55) which is *substantially the same* as the claimed crystalline process in stirring the reaction mass at 25-35 °C (room temperature) for 0.5-10 hours (overnight).

b. Rejection under 35 USC §103(a)

The gist of appellants argument is that the examiner provided no suggestion to modify, no expectation of success and provided insufficient basis to shift the burden to appellants because this is a polymorphic form.

**It is the examiner’s position:**

The examiner has carefully compared in details of the physical data of the prior art donepezil hydrochloride form III and the instant donepezil hydrochloride form VI and find that substantially similar patterns in X-ray pattern, IR pattern and DSC pattern for which a 102 was made. The obvious rejection was on the minor differences in some x-ray or IR peaks or variation in solvents, temperature etc. i.e. obvious variation in measurements.

It is like having two claims:

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One is: Benzene with b.p. at 80 °C  
Another is: Benzene with b.p. at 80.2 °C.

Is it identical? No. It is only *substantially* identical.

However, if by factual evidence, that it is known by one skilled in the art that the accuracy in measuring b.p. is  $\pm 0.5$  °C, then the two are obvious variation due to artifacts. In possession of one would suggest the possession of another because such is the sphere of obviousness that surrounds the prior art as expected by one having ordinary skill in the art.

The examiner has made due diligence in providing in the record of the extreme similarity in the physical data as found in exhibit I, II and III. The examiner further provided per ponderous of evidence that one in the crystalline polymorphic art is well aware of the inaccuracy and discrepancies occur for such measurements in X-ray etc. The burden is shifted to the appellants to show whether the product is the same with the sphere of discrepancy in physical data measurement. Or, whether appellants would provide “factual evidence” through side by side comparison using the same machine, same environment etc. to show that the claims are drawn to a new form and such new form can be reproducibly prepared to be differentiated from the old form.

c. Objection to claims 8-12

Appellants’ argument that as long as the process makes claim 2 products, variation would not be broadening. This is inconsistent with appellants’ argument of obviousness. Appellants needs to decide is polymorphic form formation limited or obvious. If making one polymorph must use concise process, then the claims are broadening since the base claim has only limited antecedent basis.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Celia Chang/  
Primary Examiner, Art Unit 1625

Conferee

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Acting Director of Technology Center 1600

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